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14. ABSTRACT
Women with hereditary breast cancer are at high risk for contralateral breast cancer (CBC). To evaluate factors influencing CBC risk in women with BRCA mutations, the funded study was designed to assess the impact of tamoxifen and radiotherapy on CBC. Records from a total of 874 Ashkenazi women with breast cancer diagnosed between 1990 and 1996 were reviewed to expand the initial cohort of 305 women treated between 1980 and 1990. Changes in medical record storage and HIPAA privacy regulations prevented the gathering of required basic clinical and/or follow-up information for an unacceptably large proportion of subjects. Because of the significant loss of patients to follow-up and lack of pathology material for genotyping, alternative methods of attaining the study goals were sought. Specifically, concatenation of the original 1980-1990 data-set with a similar ascertainment from another institution was performed, and suggested a 53% contralateral risk reduction with adjuvant tamoxifen. A further 103 patients undergoing breast-conserving treatment were analyzed. This clinical ascertainment did not clearly support a benefit from tamoxifen (HR 0.71, 95% C.I. 0.23-2.2). However, an expansion of the clinical ascertainment did suggest a benefit from tamoxifen (HR 0.37, 95% C.I. 0.35) and no negative effect from radiation.

15. SUBJECT TERMS
BRCA1, BRCA2, hereditary breast cancer, radiotherapy, tamoxifen

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Introduction

Although women with *BRCA1* or *BRCA2* mutations constitute a small minority of breast cancer patients overall, in some populations (e.g. Ashkenazi Jewish women with breast cancer before age 50), an appreciable proportion of cancers are *BRCA*-related. Women with germline mutations are at substantially increased risk of breast cancer, both *de novo* and contralaterally after a first cancer diagnosis. The study of factors influencing the development of contralateral cancer in such women may provide important clues as to the risks and benefits of certain prevention strategies for unaffected individuals. Exposures that promote the development of contralateral disease should likely be avoided by both affected and unaffected heterozygotes, while interventions that reduce contralateral risk are obvious candidates for deployment in the primary prevention arena. Unfortunately, survival and selection biases may confound the study of variables modulating contralateral risk in prevalent groups of women with *BRCA* mutations, who are usually identified through familial cancer clinics. The present study, employing a retrospective anonymized design, was intended to circumvent those biases and allow the collection of a relatively unselected group of women with *BRCA* mutations for the examination of factors influencing contralateral risk.

Body

To accomplish the aims of the funded project, we extended our previous work examining outcomes in Ashkenazi women with invasive breast cancer. In our original publication, performed without DOD funding, we reported local control and systemic outcomes in Ashkenazi women with breast cancer treated at our institution with lumpectomy and adjuvant radiotherapy between 1980 and 1990, comparing the clinical outcomes of women with or without germline founder mutations in *BRCA1* or *BRCA2*. A retrospective, anonymized design was employed to address the difficult human subjects issues relevant to germline predisposition research. Once notice was received of funding for extension of the project, we first reviewed the initial cohort and determined the impact of tamoxifen on contralateral cancer risk among the mutation carriers in that study. There were 25 mutation carriers for whom tamoxifen use was known. There was 1 metachronous contralateral cancer among 5 mutation carriers taking tamoxifen, and 6 among the 20 carriers not taking tamoxifen (HR 0.57[95% CI: 0.07-4.57; P=0.6]).These data were presented at the 2002 Era of Hope meeting.[1]

Subsequently, local IRB and Department of Defense HSRRB approval was obtained to allow records review and tissue acquisition from

Ashkenazi women receiving treatment (either lumpectomy and radiation, or mastectomy with or without adjuvant radiation) for invasive breast cancer between 1990 and 1995 at Memorial Sloan-Kettering. Final approval to initiate this expansion was received at the end of August 2001, and contracting was completed by 30 October of that year. In accordance with the Statement of Work agreed upon, from October 2001-March 2002, institution databases were reviewed to identify women diagnosed with invasive breast cancer in that interval from 1990-1992. Hospital registration databases were cross-referenced to identify women of self-reported Jewish religious preference (an effective surrogate for Ashkenazi ancestry in our patient population). Over 800 Jewish women were treated for invasive breast cancer at Memorial Sloan-Kettering in 1990, 1991, and the first half of 1992. Of those, 422 had pathology material available, the remainder having received primary surgical therapy elsewhere. Unfortunately, medical records were only retrievable for 25% of these patients. It was found that, after our institution converted to an electronic medical record system in 1998, it became extremely difficult to access medical records for women who had become inactive patients. Women who were survivors were more likely to have active records, which were retrievable. This raised concerns that the ascertainment would become subject to a "survivor bias." Follow-up data were also inconsistently available as many of the subjects were not considered "analytic cases" by the hospital tumor registry, their initial biopsy diagnosis having been made elsewhere before referral to our institution for definitive treatment. Traditional means of obtaining follow-up on such patients, such as calling their local physicians, are now prohibited by HIPAA regulation.

In response to the difficulties encountered in retrieving records from 1990-1992, the ascertainment was expanded, and records for women diagnosed between 1992 and 1996 were reviewed. Based upon this expansion, as described in the November 2003 Annual Report, we identified 452 additional women with pathology material theoretically available for genotyping. We anticipated beginning genotyping in February 2004, and completing the data analysis by June 2004. Unfortunately, similar problems with follow-up were encountered with the expanded data set. Recent follow-up data (within 4 years) were unobtainable for 78 patients (17%), with critical treatment information being found to be missing in a substantially greater number of cases. Again, recently evaluated patients are, by definition, survivors, were more likely to have retrievable records and the lack of follow-up information of a substantial proportion of the remaining cases posed a very risk of introducing a survival bias into the analysis. Records have been requested on several occasions from the institutional archival retrieval service, without response as yet.

The difficulties completing the clinical follow-up resulted in falling behind the schedule in the project Statement of Work. We requested a 1-year no-cost extension to this project to allow us to further pursue the relevant records and follow-up information prior to anonymizing and performing the genotyping. Unfortunately, these efforts were unsuccessful. Clinical information and/or pathology specimens were unavailable for a large proportion of cases. As the outcome of the study was likely to be hopelessly confounded by the Neyman bias introduced by the mere fact of availability of material and follow-up, the retrospective anonymized design has been found to be unfeasible.

Given the difficulties encountered in developing the cohort for anonymized study, two different approaches were taken to address the study goal of identifying factors associated with contralateral cancer risk in *BRCA* mutation carriers, and particularly the potential benefit of tamoxifen. First, data from our first anonymized series were combined with a similar series from the Jewish General Hospital in Montreal. The combined series comprised 496 women who underwent breast conserving treatment for 520 breast cancers. There were a total of 56 mutation carriers. The clinical characteristics of mutation carriers and non-carriers are presented in table 1.

Table 1.

Variable	No *BRCA* founder mutation (n=439)	*BRCA1* founder Mutation (n=43)†	P (*BRCA1* vs. no founder mutation)*	*BRCA2* founder mutation (n=14)†	P (*BRCA2* vs. no founder mutation)*
Age at Diagnosis					
< 50	135 (31%)	30 (70%)	< 0.0001	4 (29%)	NS
≥ 50	305 (69%)	13 (30%)		10 (71%)	
Tumor Size					
T1	324 (74%)	29 (67%)		8 (57%)	
T2	97 (22%)	11 (26%)	NS	4 (29%)	NS
Unknown	19 (4%)	3 (7%)		2 (14%)	
Nodal Involvement					
Present	149 (34%)	18 (42%)		6 (43%)	
Absent	262 (60%)	23 (53%)	NS	6 (43%)	NS
Unknown	29 (6%)	2 (5%)		2 (14%)	
Estrogen Receptor					
Positive	197 (45%)	6 (14%)		7 (50%)	
Negative	98 (22%)	27 (63%)	< 0.0001	3 (21%)	NS
Unknown	145 (33%)	10 (23%)		4 (29%)	
Chemotherapy					
Yes	155 (35%)	24 (56%)		7 (50%)	
No	241 (55%)	17 (40%)	0.03	7 (50%)	NS
Unknown	45 (10%)	2 (4%)		0 (0%)	
Tamoxifen					
Yes	187 (43%)	10 (23%)		9 (64%)	
No	195 (44%)	30 (70%)	0.01	5 (36%)	NS
Unknown	45 (10%)	3 (7%)		0 (0%)	

All contralateral breast cancer diagnoses were considered new primary lesions for the purposes of calculating the cumulative incidence of contralateral breast cancer. Women who had undergone contralateral mastectomy prior to the breast cancer diagnosis for which they underwent breast conservation (n = 7) were excluded from the analysis of this endpoint. Patients were censored if they had not experienced the endpoint of interest at the time of last follow-up. Kaplan-Meier estimates of time free from contralateral breast cancer were compared using the log-rank test. A Cox proportional hazards model was used to estimate the hazard ratios (HR) for contralateral breast cancer-free survival time under a multivariate model after accounting for death due to causes other than breast cancer as a competing risk. The cumulative incidences of the endpoints in women with and without mutations were compared using a chi-square test fit using the method of Gray. *P* values comparing the overall curves corresponding to the endpoint of interest are provided for these univariate comparisons. Multivariate proportional hazards models accounting for non-breast cancer death as a competing risk were fit using the method of Fine and Gray. All *P* values were calculated with two-sided tests. The relative risk of contralateral breast cancer in mutation carriers receiving tamoxifen, compared to those not receiving tamoxifen, was 0.47 (95% C.I. 0.14-1.59; *P*= 0.23).[2] Figure 1 illustrates the difference in CBC risk between carriers and non-carriers.

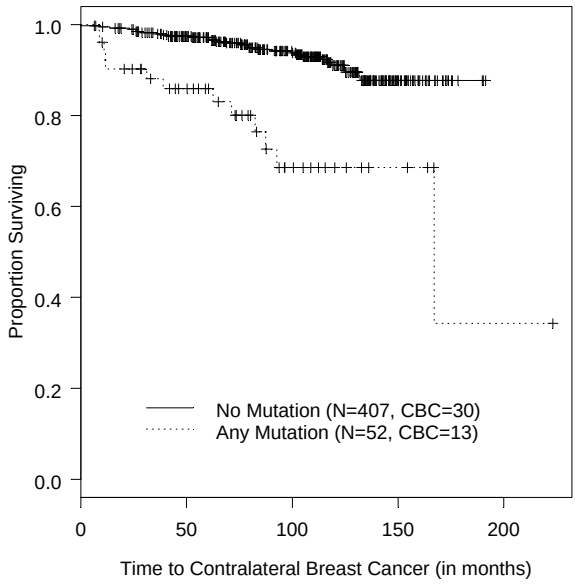


Figure 1. Risk of contralateral metachronous disease

DOD support was specifically acknowledged in this publication.

Second, a clinic-based ascertainment of affected *BRCA* mutation carriers was reviewed and clinical data extracted to determine outcomes in women undergoing breast-conserving therapy. In this clinic-based ascertainment, which does not significantly overlap with the previous Ashkenazi ascertainment or with the un-selected 1990-1996 ascertainment, there were 103 carriers who were initially treated with breast-conserving intent for 115 breast cancers. The clinical characteristics of the patients included in this study are presented in table 2.

Table 2.

Feature	*Patients (n= 87)*	*Cancers (n=95)*
Mutation		
BRCA1	62 (71.3%)	68 (71.6%)
BRCA2	25 (28.7%)	27 (28.4%)
Age at initial diagnosis	Median 43 years (27-82)	
Diagnosis to testing interval	Median 34 mo (-60-225)	
Family history		
First-degree	64 (73.6%)	
Second-degree only	14 (16.1%)	
None	9 (10.3%)	
Histology		
Infiltrating ductal, NOS		84 (88.4%)
Medullary/atypical medullary		7 (7.4%)
Tubular		1 (1.1%)
Infiltrating Lobular		3 (3.2%)
Tumor size		Median 1.4 cm (0.1-5.0)
T stage		
T1		71 (74.7%)
T2		22 (23.2%)
Unknown		1 (1.1%)
Histologic Grade		
I		2 (2.1%)
II		7 (7.4%)
III		70 (73.7%)
Unknown		16 (16.8%)

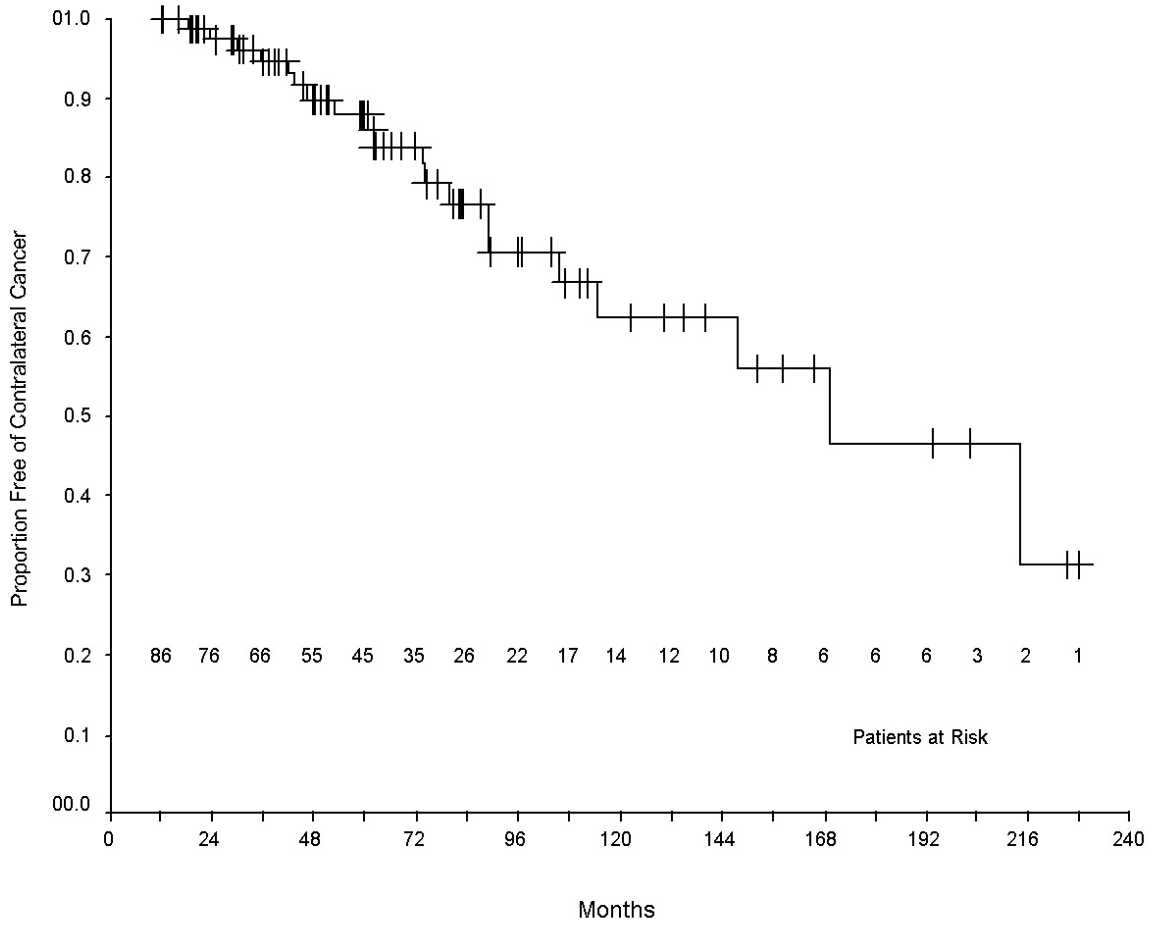
Hormone receptor (ER or PR)	
Positive	34 (35.8%)
Negative	45 (47.4%)
Unknown	16 (16.8%)
Axillary nodes	
Positive	28 (29.5%)
Negative	63 (66.3%)
Unknown	4 (4.2%)
Radiation Dose	
Whole breast	Median 46.8 Gy (40-54)
Boost	Median 14 Gy (0-22.8)
Treatment	
Chemotherapy (± tamoxifen)	70 (73.7%)
Tamoxifen (± chemotherapy)	28 (29.5%)

Survival data were calculated by the method of Kaplan and Meier, in this case without correction for competing causes of death. Freedom from metachronous contralateral breast cancer (CBC) was defined as the time from first breast cancer diagnosis to the time of pathologic diagnosis of contralateral cancer, or last follow-up. Univariate analyses evaluating the effect of patient characteristics and clinical variables on time to the endpoint of interest (metachronous contralateral cancer) were performed utilizing two-sided log rank tests. For continuous variables such as age and time from diagnosis to genetic testing, comparisons between groups were performed using non-parametric tests. All *P* values are two-tailed, with α=0.05. Statistical analyses were performed using SPSS for Windows, version 10.0 (SPSS Inc, Chicago, IL).

Of the 87 women in this study, 20 (23.3 %) developed a contralateral breast cancer (CBC) at a median of 67.4 months (range 18.6-214.4) months after their first diagnosis. The crude average annual incidence of CBC was 39.3 per 1000 woman-years. The 5-, 10-, and 15-year probabilities of remaining free of CBC were 88.1%, 62.4%, and 46.8%, respectively (Figure 2). In 15 cases (75.0%) the contralateral cancers were diagnosed in *BRCA1* mutation carriers, and in 5 cases (25.0%) in *BRCA2* mutation carriers. Age at first breast cancer diagnosis, gene mutation (*BRCA1 vs. BRCA2),* hormone receptor status, histologic grade, and treatment (chemotherapy and/or tamoxifen) were all examined as possible predictors of CBC in *BRCA* mutation carriers. None were

statistically significantly associated with CBC. The mean interval from initial diagnosis to genetic testing was longer in women with CBC than in those without (81.1 months vs. 39.4 months; *P*= 0.001), but there was no difference in the probability of being free of CBC at 5 years in women whose initial diagnosis was made less than 2 years before testing, compared to those whose index diagnosis was made 2 or more years before testing (85.8% vs. 89.4%; logrank *P*=0.60).

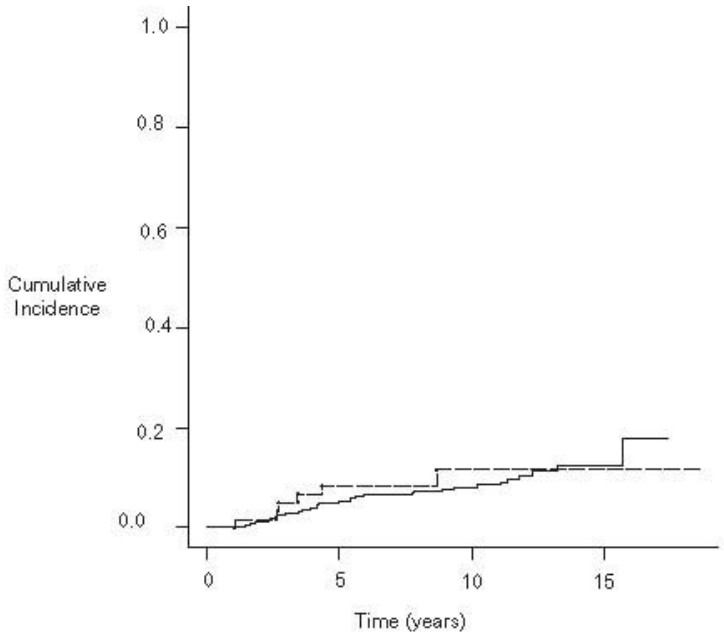
Figure 2. Probability of remaining free of contralateral cancer



In this series, there were no statistically significant differences in the 5- or 10-year risk of contralateral breast cancer between the 37 mutation carriers who received tamoxifen for their index breast cancer and the 64 women who did not. Tamoxifen status was unknown for 2 women. These results were presented at the 2004 Annual Meeting of the American Society of Clinical Oncology in New Orleans, LA,[3] and subsequently published in the journal *Cancer* in 2005, acknowledging DOD support.[4]

Although the DOD-funded project that supported the above studies was not intended to examine the issue of ipsilateral cancer risk after breast conservation in BRCA mutation carriers, the methods used to examine the research question of contralateral risk were also applied to the question of ipsilateral recurrence risk. Both of these cohorts were limited to women who had undergone limited excision and adjuvant radiation therapy as primary treatment. In the combined analysis retrospective cohort study,there was no significant difference between women with and without *BRCA* mutations in the risk of metachronous ipsilateral breast cancer at 10 years (12% in women with mutations *vs* 8% in women without; *P* = 0.68) (Figure 3). Age less than 50 years at initial diagnosis was the only significant predictor of metachronous ipsilateral disease (*P* = 0.002).[2]

Figure 3. Metachronous ipsilateral cancer risk in carriers vs noncarriers



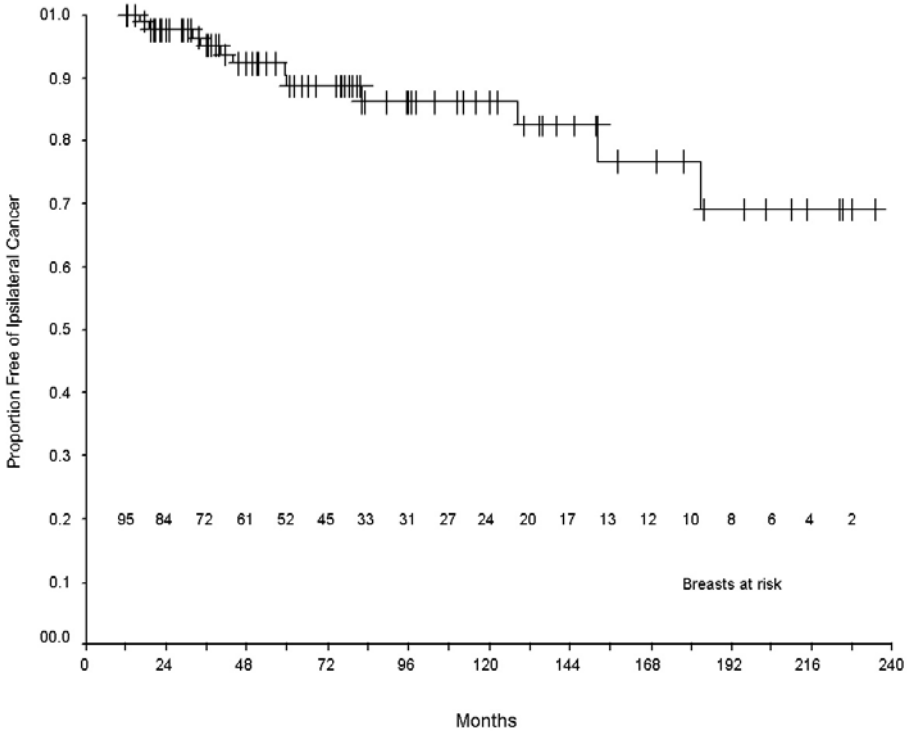
Breasts at risk						
	Year 1	Year 3	Year 5	Year 10	Year 12	Year 15
Mutation present	61	48	39	10	5	5
Mutation absent	453	417	375	172	94	94

Breast Cancer Research

In the prevalent ascertainment,[4] metachronous ipsilateral breast cancers (MIBC) were diagnosed after treatment of 12 (12.6%) invasive breast cancers at a median of 51.8 months after initial diagnosis (range 16.2-182.7 months). The crude average annual incidence of MIBC was 18.2 per 1000 woman-years. The 5-, 10-, and 15-year probabilities of remaining free of MIBC were 88.8%, 86.4%,

and 76.6%, respectively (Figure 4).

Figure 4. Metachronous ipsilateral risk in prevalent ascertainment



Of the 12 MIBC, 8 (66.7%) were DCIS and 4 (33.3%) were invasive carcinomas, suggesting a possible benefit to screening for early detection. In 7 cases (58.3%) the MIBC were diagnosed in *BRCA1* mutation carriers, and in 5 cases (42.7%) in *BRCA2* carriers. Age at diagnosis, gene mutation (*BRCA1 vs. BRCA2),* tumor size, nodal status, hormone receptor status, histologic grade, and treatment (chemotherapy and/or tamoxifen) were all examined as possible predictors of MIBC in *BRCA* mutation carriers with invasive disease who received radiation. None were statistically significantly associated with MIBC. The mean interval from initial diagnosis to genetic testing was longer in women with MIBC than in those without (74.9 months vs. 43.1 months; *P*= 0.04).

The results of these studies were among the strongest available at the time indicating that breast conserving therapy remained an appropriate option for BRCA mutation carriers, so long as those women were willing to accept the high risk of metachronous contralateral disease.

We also made another attempt to address the original study questions by utilizing a clinically ascertained group to address the study questions, accepting the inherent survival bias of this approach. In the last year of the project, we expanded the clinic-based ascertainment to include women with mutations treated with either mastectomy or breast-conserving treatment. The MSKCC Clinical Genetics Service has enrolled 257 women with germline *BRCA* mutations and invasive breast cancer on follow-up studies between May 1992 and March 2005. It should be noted that a recent multi-institutional collaboration accrued 469 mutation carriers, demonstrating that our single-institutional experience is quite substantive, and clinically well characterized as all records are available to us. Median follow-up in our series is 86.9 months for surviving women, providing a significant number of women-years at risk to address variables associated with contralateral cancer risk. As in previous studies from our institution and others, the risk of contralateral breast cancer was high in these women, with 27.1% of women developing contralateral disease by 10 years of follow-up (12.5% at 5 years). Log-rank comparisons of survival curves and Cox proportional hazards analysis was used to evaluate the possible association of several factors with the risk of contralateral cancer. The 10-year risk of contralateral cancer among the 72 women receiving adjuvant tamoxifen was 12.5%, compared to 31.4% among the women not receiving tamoxifen (log-rank P=0.02). By Cox regression analysis, the HR for women taking tamoxifen was 0.35 (95% C.I 0.14, 0.89). A similar benefit was observed when the analysis was stratified by germline mutation (BRCA1 or BRCA2). We found no significant benefit of oophorectomy in terms of contralateral risk reduction, which is different from what has been reported by other groups. In addition, there was no increase in CBC risk among women undergoing lumpectomy versus those undergoing mastectomy, or among all women receiving adjuvant RT compared to those who did not. There was no difference in CBC risk among women diagnosed with their index cancer before or after the age of 50, pre- or post-menopausally, or as a result of BRCA1 as opposed to BRCA2 mutations. These results suggest that women with mutation receiving tamoxifen as adjuvant treatment for their index breast cancer experience a substantial benefit in terms of contralateral risk reduction. The results also do not indicate that women receiving adjuvant radiotherapy experience any increase in contralateral risk.

Key Research Accomplishments

- Determined that the relative risk of contralateral breast cancer in mutation carriers receiving tamoxifen, compared to those not receiving tamoxifen, was 0.47 (95% C.I. 0.14-1.59; *P*= 0.23) in a combined analysis of two retrospective anonymized cohort studies involving 497 women of Ashkenazi ancestry and 56 mutation carriers identified without regard to survival or family history.
- Determined that the risk of contralateral cancer in mutation carriers was significantly higher than that of non-mutation carriers.
- Determined that tamoxifen use was associated with a significantly lower risk of contralateral breast cancer in a prevalent series of 256 mutation carriers, althoughtreatment was not randomly assigned and thus attribution could not be established with confidence.
- Determined that ipsilateral metachronous cancer risk was similar in carriers compared to non-carriers in both a retrospective anonymized cohort (direct comparison) and a prevalent cohort (historical controls), thus supporting breast conserving treatment as a reasonable and appropriate option for mutation carriers.

Reportable Outcomes

- Robson M, Satagopan J, Boyd J, Offit K. Impact of Tamoxifen on the Risk of Metachronous Contralateral Breast Cancer (CBC) in Women with Germline Mutations of BRCA1 or BRCA2. Era of Hope Meeting, Orlando, Florida, September 25 – 28, 2002

- Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Bégin LR, Offit K, Foulkes WD. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 2004, 6:R8-R17

- M Robson, T. Holcombe, B. McCormick, P.Borgen, C. Hudis, N. Kauff, T. Gulati, S. Jhanwar, L. Norton, K. Offit. Feasibility of Breast Conserving Treatment for Breast Cancer in Women with Germline BRCA Mutations: A Clinic-Based Series. J Clin Oncol 2004;22 (14S): 864s (abstract 9618)

- Robson M, Svahn T, McCormick B, Borgen P, Hudis CA, Norton L, Offit K. Appropriateness of breast conserving treatment for breast cancer in women with germline mutations in BRCA1 or BRCA2: A clinic-based series. Cancer 2005;103:44-51

Conclusions

The goal of the project was to evaluate the impact of tamoxifen and radiotherapy on contralateral breast cancer risk in women with germline mutations in *BRCA1* and *BRCA2*. Previous studies have been confounded by potential survival bias, and an anonymized retrospective design was therefore proposed. The implementation of this design was severely hampered by difficulty retrieving clinical data caused by changes in the medical record management practices, and specifically conversion to an electronic medical record. In addition, obtaining recent follow-up information on patients diagnosed over a decade ago, but no longer followed at MSK, was found to be very difficult due to HIPAA regulations which restrict external physicians from providing follow-up information. This raised the possibility of introduction of the same survival bias that the anonymized design is intended to circumvent, as only survivors have recent follow-up at our institution. The situation could potentially be even worse than in a clinical ascertainment, as the attempt to ascertain women diagnosed a relatively long time ago (in order to maximize follow-up) meant that only very long-term survivors had follow-up. These difficulties have led the project to fall behind schedule, and eventually necessitated the use of alternative approaches to address the study hypotheses.

Given the difficulties encountered in realizing the original anonymized design, the specific aims of the project were addressed through alternative means. First, a collaboration was established with Jewish General Hospital (Dr. William Foulkes), and data from the two similar retrospective anonymized cohorts were combined. This allowed an approximate doubling of the number of mutation carriers available for study, which continued to suggest a benefit in terms of contralateral risk reduction from tamoxifen, although, even in the expanded data-set, the numbers were insufficient to achieve statistical significance. In addition, a non-overlapping clinic-based cohort was analyzed, which initially failed to suggest a similar tamoxifen benefit. When the clinical ascertainment was enlarged, however, a tamoxifen benefit became evident and, furthermore, it became possible to address the possibility of an adverse effect of radiation, which was not observed.

In conclusion, the work performed under this contract has supported the existence of a benefit from tamoxifen in reducing contralateral breast cancer risk in women who receive the drug for their index

breast cancer. We have not demonstrated any negative effect of adjuvant radiation on contralateral risk. The specific aims were addressed using alternative approaches when it became evident that the originally planned approach was being delayed by unanticipated administrative and regulatory complications.

References

[1] Robson M, Satagopan J, Boyd J, Offit K. Impact of Tamoxifen on the Risk of Metachronous Contralateral Breast Cancer (CBC) in Women with Germline Mutations of BRCA1 or BRCA2. Era of Hope Meeting, Orlando, Florida, September 25 – 28, 2002

[2] Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Bégin LR, Offit K, Foulkes WD. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res 2004, 6:R8-R17

[3] M Robson, T. Holcombe, B. McCormick, P.Borgen, C. Hudis, N. Kauff, T. Gulati, S. Jhanwar, L. Norton, K. Offit. Feasibility of Breast Conserving Treatment for Breast Cancer in Women with Germline BRCA Mutations: A Clinic-Based Series. J Clin Oncol 2004;22 (14S): 864s (abstract 9618)

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Appendices

None